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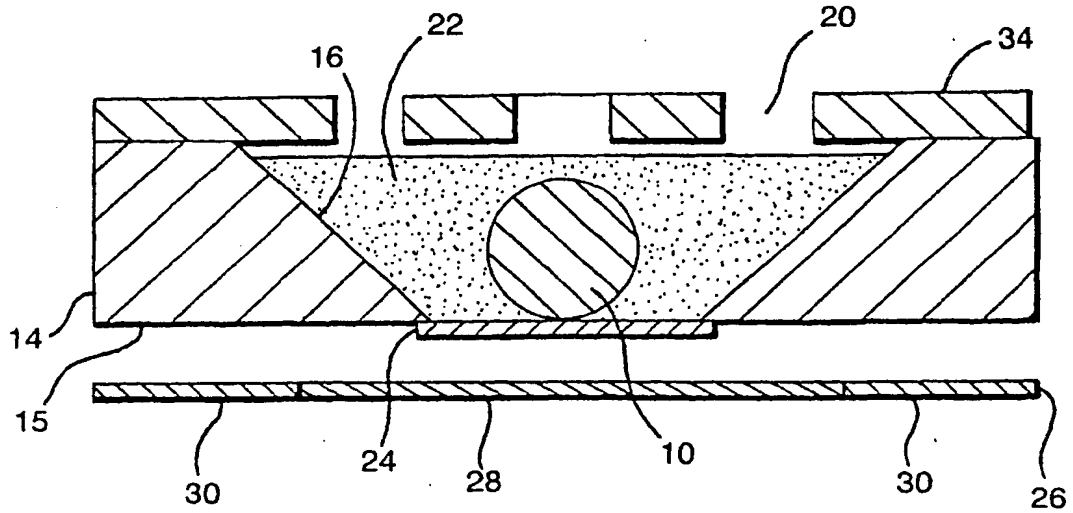
(54) Title: METHOD OF AND APPARATUS FOR REMOVING A SUBSTANCE FROM A CONTAINER



(57) Abstract

A bead (10) holding a chemical compound is situated in a well (12) of a micro–titre plate (14). A liquid (22) is introduced into well (12) and the chemical compound is released into the liquid. The liquid (22) and the chemical compound may be removed from the well (12) by bringing a capillary membrane (26) into contact with the well (12). Liquid (22) is drawn into the capillary membrane (26) via capillary action. Membrane (26) has areas of hydrophobicity (30) defined thereon so that the liquid (22) and the compound are drawn into predefined areas of the membrane (26). The membrane (26) can be dried and rehydrated at a later date in order to screen the compounds for activity, or it may form the base of an array of wells of a further micro–titre plate. Screening for compounds of interest may then take place either on the sheet, or with the sheet forming the base of the further micro–titre plate.

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METHOD OF AND APPARATUS FOR REMOVING A SUBSTANCE FROM A CONTAINER

Technical Field

The present invention relates to a method of and apparatus for removing a substance from a container. It relates particularly, but not exclusively, to removing a substance which has been formed via a combinatorial process.

Background Art

Combinatorial chemistry is a technique whereby many different chemical compounds are synthesised by multiple chemical reactions. A library of chemical compounds may be formed on solid phase supports. The solid phase supports are commonly known as beads. Beads of the size approximately a tenth of a millimetre in diameter are typically used in such reactions. Libraries of chemical compounds are usually formed on a large number of beads. It is desirable to label each chemical compound of libraries in order to identify the chemical compound of interest attached to the beads. Such identifiers may be physical or chemical. Physical identifiers may be in the form of a bar code or similar optical code (which may be applied to the bead by means of a laser), or an RF device.

Following synthesis of the library of chemical compounds, the next stage is screening the compounds. This may be achieved by a method known as high-throughput screening (HTS). In HTS, the library (or a subset of the library) is reacted with a target compound in order to determine which compounds of the library show activity. Such reactions are usually performed with the chemical compounds being in an aqueous solution, rather than bound to a bead. As a result, the synthesis route of the chemical compounds may not be easily identified.

A method of transferring a chemical compound from a bead for further screening is disclosed in International Patent Application No. WO-A1-9715394 (Smithkline Beecham). In this method, the walls of wells formed in a micro-titre plate are coated with a binding surface on which compounds may be synthesised. The wells are then used to

dispense the compounds synthesised in the wells into a further vessel for screening. The compounds are dispensed by applying pressure to the liquid in the wells causing it to jet out of the hole into the further vessel. A disadvantage of this method is that due to the very small volumes of fluid transferred, fluid may evaporate and not be transferred to the receiving container.

An aim of the present invention is to simplify the transfer of chemical compounds formed via a combinatorial process from a container into a further container. Another aim of the invention is to transfer simplify the transfer of chemical compounds formed via a combinatorial process from a container into a further container for high-throughput screening, while still allowing the synthesis route of a compound being screened to be determined.

Disclosure of Invention

According to a first aspect of the invention there is provided a method of removing a substance from a container, the method comprising the steps of: a) introducing a fluid, preferably a liquid, into the container so that at least a portion of the substance is taken up by the fluid, and b) removing the fluid and the substance from the container by placing a sheet of absorbent material in sufficiently close proximity to the container so that the fluid and the substance are absorbed by the sheet and substantially retained by the sheet.

Preferably the sheet and the container are separated one from another after an amount of fluid has been absorbed by the sheet. The sheet containing the fluid and the substance (which may be a compound) may then be dried, so that the substance is retained on the sheet in a dry form. The sheet may then be rehydrated at a later date. The substance associated with the sheet may then be screened in order to identify substances of interest or activity.

The sheet may have hydrophobic portions defined on it, so that the fluid and the substance are guided to, or maintained within, predetermined locations on the sheet.

The sheet may then be affixed to the further container. The further container preferably has an array of wells formed therein. Preferably the base of a well is defined by the sheet.

Alternatively, the openings of the wells may be covered by the sheet. Fluid may be "washed" through the absorbent sheet so that the substance attached to the sheet and the wash fluid are introduced into the wells of the further container. Screening for substances of activity or interest may then take place.

A substantially hydrophobic sheet may be bonded to the absorbent sheet either before it is affixed to the further container, or after it has been attached. Fluid, preferably a liquid, may then be added to the wells of the further container via the openings of the wells. The hydrophobic sheet may thus prevent leakage of the fluid from the base of the well via the absorbent sheet.

Preferably the sheet, whether it be mainly hydrophobic or porous, is affixed to a container by adhesive, curing, mechanical fixing, heating, ultrasonic welding, or a combination of these techniques.

Preferably the container and/or the further container is a specially adapted 96- or 384-well micro-titre plate. The container preferably has the same dimensions as a standard laboratory micro-titre plate, each well of the plate having a small aperture in its base, or its base being defined by a fine mesh.

According to a second aspect of the invention there is provided an apparatus for removing a substance from a container, the apparatus comprising: an absorbent sheet, the sheet having defined thereon a plurality of hydrophilic regions whose boundaries are defined by hydrophobic portions, the hydrophilic regions being dimensioned and arranged so that they are capable of receiving contents from a plurality of wells formed in the container.

Preferably the absorbent sheet is a capillary membrane. It may be, for example, a Pall Gelman Predator™ membrane. The volume of fluid removed from the container is determined by the capacity of the membrane, and the dimensions of the hydrophilic areas defined on the membrane.

These hydrophobic areas may be defined by heating sealing, or by printing of a polymer. The polymer may be wax, or a wax/polymer mixture. Preferably the hydrophobic portions

define an array of hydrophilic cells on the sheet, the hydrophilic cells being dimensioned and arranged so that they are congruous with an array of wells formed in a container.

According to a third aspect of the invention there is provided a container comprising a plurality of wells, the base of a well having at least one aperture, the at least one aperture being dimensioned so as to retain liquid in the well by way of surface tension.

The container preferably has defined therein an array of wells. The wells may be defined by tapered walls, a base, and have an opening to allow the introduction of a fluid or an article into a well. The exterior surface of the base of the wells may be hydrophobic so as to guide the fluid to a desired location.

The wells may have at least one aperture defined in their bases. The at least one aperture is dimensioned so that liquid may be retained in the well via surface tension. Preferably the at least one aperture is less than 1 mm in diameter. Most preferably the at least one aperture is less than 0.1 mm in diameter. However, the apertures may have a considerably smaller aperture than this, for example, 25 microns in diameter. Alternatively, the base of a well may be formed by a fine mesh.

The container may have the same dimensions as a standard laboratory micro-titre plate, each well of the micro-titre plate having a small aperture in its base, or its base being defined by a fine mesh.

According to a further aspect of the invention there is provided a system for removing a substance from a container, the system comprising: a) means for locating at least one article, the at least one article having the substance associated therewith; b) placing means for introducing the at least one article into at least one well defined in a first container, the well having at least one aperture; c) fluid introducing means for introducing fluid into the at least one well; d) chemistry releasing means for releasing at least a portion of the substance into the fluid; and e) means for bringing an absorbent sheet in sufficiently close proximity to the at least one well so that the fluid and the substance are drawn onto and subsequently retained by the absorbent sheet.

The system may also include separating means for substantially separating the absorbent sheet from the first container. A drying means may also be provided for drying the absorbent sheet, thereby retaining at least a portion of the substance on the absorbent sheet.

Preferably the system includes an affixing means for affixing the absorbent sheet to a further container, the further container having a plurality of wells formed therein.

The substance is preferably supported by a solid-phase support such as a resin bead. The substance has preferably been formed by a combinatorial process. The resin bead may have a tag attached to it identifying the synthesis steps that the bead has undergone. This tag may be a physical tag such as an alpha-numeric code, a bar code, or an RF tag.

Methods for releasing a chemical compound from a bead into a fluid are well known in the art. These methods may release all of the chemical compound from the bead, or only a portion of the compound may be released, the rest remaining bound to the bead. For example, a well-known method is the use of a linker (which links the compound to a bead) which is disrupted by shining UV light onto the bead.

According to a further aspect of the invention there is provided a substance removed from a container using the method and/or apparatus previously described.

According to another aspect of the invention there is provided a substance removed from a container by way of the system previously described.

Brief Description of Drawings

A number of embodiments of the invention will now be described, by way of example only, with reference to the accompanying Figures, in which:-

Figure 1 shows an isometric view of a capillary membrane sheet;

Figure 2 shows a cross-sectional view of a bead within a well;

Figure 3 shows a cross-sectional view of a capillary membrane sheet being brought into contact with a well;

Figure 4 shows a cross-sectional view of a liquid from a well being drawn into a capillary membrane sheet;

Figure 5 shows a cross-sectional view of a capillary membrane sheet being separated from a well; and

Figure 6 shows a cross-sectional view of a capillary membrane sheet bonded to form the base of a well.

Best Modes for Carrying Out the Invention

A number of embodiments of the invention will now be described with reference to Figures 1 to 6. Referring to Figure 2 of the drawing, a sectional view of a bead 10 within a well 12 is shown. The well 12 shown in Figure 2 is defined by tapered walls 16, a base 18 and an opening 20. The exterior surface 15 of the base of a well may be hydrophobic. An array 14 of such wells 12 may comprise a micro-titre plate which is specially adapted for use with the apparatus. That is, each well of the micro-titre plate has an aperture in its base, or its base may be defined by a fine mesh.

A chemical compound has been formed on the bead 10. The compound may have been formed on the bead 10 during a combinatorial process. Bead 10 may have attached thereto a physical tag to enable the synthesis steps of the chemical compound to be identified. If the physical tag is an optical code, the optical code may be read from the bead 10 while bead 10 is situated in well 12.

A liquid 22 is added to the well 12 via the opening 20, as shown in Figure 3. Alternatively, the liquid 22 may be present in the well 12 when the bead 10 is added. The chemical compound held by the bead 10 is released into the liquid 22. The chemical compound may be released by agitating the array of wells 14, heating the liquid 22 in the well 12, or by shining UV light onto the bead 10. Other methods for releasing chemical compounds synthesised on solid phase supports such as beads are well known in the art and may also be used. A cover 34 may be bonded or attached to the array 14 to cover the opening 20 of well 12 to stop the bead 10 from escaping from the well.

In this example, the base of the well 12 is formed from a fine mesh 24, such that the liquid 22 remains in the well 12 by the liquid's surface tension. Alternatively, a single aperture may be formed in the base 18 of the well 12. The diameter of the single aperture may be dimensioned such that liquid 22 is held in well 12 via surface tension.

Capillary membrane sheet 26 is then brought into contact with the base of the well 12, as shown in Figure 4. An isometric view of capillary membrane sheet 10 is shown in Figure 1. An array of porous cells 28 are defined on the sheet by hydrophobic areas 30. The porous portions of the membrane typically have areas ranging from 50 μm^2 to 2 mm^2. The dimensions of these defined areas will obviously depend upon the size of the wells of the micro-titre plate. Membrane 26 is typically approximately 50 to 200 μm thick, with an open pore volume of 80% to 90%. Hence one can consider removing volumes of liquid of the order of 100 picolitre to 720 nanolitre.

The 22 liquid containing the chemical compound flows from the well 12 into the porous areas 28 of capillary membrane sheet 26, according to the capacity of the porous areas 28. When the fluid holding capacity of the membrane 26 has been exceeded, flow of liquid 22 from the well ceases and the membrane 26 is separated from the well 12. This is shown in Figure 5. An amount of the liquid is retained within the membrane 26. In the case of only part of the liquid being absorbed by the membrane 26, a further membrane, and even subsequent membranes, may be brought into contact with the well 12 in order to remove all of the liquid, and hence all of the chemical compound from the well. At this stage, membrane 26 may be dried and rehydrated at a later date in order to screen the compounds for activity.

Figure 6 indicates the membrane 26 (bearing the chemical compound) bonded to form the base of a well 38 in a further multi-well plate 36. Liquid may then be added to well 38 via the opening of the well, or through the membrane 26 itself, carrying the chemical compound and the liquid into the well where the compound may be screened for activity. Membrane 26 is shown having a hydrophobic membrane 32 bonded to its underside. This ensures that leakage of the fluid from the well via membrane 26 is prevented.

The invention has been described by way of a number of embodiments and it will be appreciated that variation may be made to the aforementioned embodiments without departing from the scope of the invention.

Claims

1. A method of removing a substance from a container, the method comprising the steps of: a) introducing a fluid, preferably a liquid, into the container so that at least a portion of the substance is taken up by the fluid, and b) removing the fluid and the substance from the container by placing a sheet of absorbent material in sufficiently close proximity to the container so that the fluid and the substance are absorbed by the sheet and substantially retained by the sheet.

2. A method according to claim 1 including the step of drying the sheet, retaining the fluid, so that the substance is retained thereon.

3. A method according to claim 1 or 2 wherein the substance is guided to, or held within, predetermined locations on the sheet.

4. A method according to claim 3 wherein the substance is guided to, or held within, predetermined locations on the sheet by way of hydrophobic portions defined on the sheet.

5. A method according to claim 1 or 2 including the step of affixing the sheet to a further container, the further container having an array of wells formed therein whereby the base of a well is substantially defined by a hydrophilic portion of the sheet, so that the substance may be transferred from the sheet to the further container.

6. A method according to claim 5 wherein the absorbent sheet is affixed to the further container by any one of the following methods taken from a) gluing, b) curing, c) mechanical fixing, d) heating, and e) ultrasonic welding.

7. A method according to any preceding claim which is used to screen a chemical compound from a member of a library of chemical compounds formed via a combinatorial process.

8. Apparatus for removing a substance from a container, the apparatus comprising: an absorbent sheet, the absorbent sheet having defined thereon a plurality of hydrophilic regions whose boundaries are defined by hydrophobic portions, the hydrophilic regions

being dimensioned and arranged so that they are capable of receiving contents from a plurality of wells formed in the container.

9. Apparatus according to claim 8 wherein the absorbent sheet is a capillary membrane.

10. Apparatus according to claim 8 or 9 wherein the hydrophobic portions of the absorbent sheet are formed by heat sealing.

11. Apparatus according to claim 8 or 9 wherein the hydrophobic portions of the absorbent sheet are formed by printing of a polymer.

12. Apparatus according to claim 11 wherein the polymer is wax, or a wax/polymer mixture.

13. A container comprising a plurality of wells, the base of a well having at least one aperture, the at least one aperture being dimensioned so as to retain liquid in the well by way of surface tension.

14. A container according to claim 13 wherein the diameter of the aperture is less than 0.1 x 10^{-3}m.

15. A container according to claim 14 wherein the diameter of the aperture is less than 25 x 10^{-6}m.

16. A system for removing a substance from a container, the system comprising: a) means for locating at least one article, the at least one article having the substance associated therewith; b) placing means for introducing the at least one article into at least one well defined in a first container, the well having at least one aperture; c) fluid introducing means for introducing fluid into the well; d) chemistry releasing means for releasing at least a portion of the substance into the fluid; and e) means for bringing an absorbent sheet in sufficiently close proximity to the well so that the fluid and the substance are drawn onto and subsequently retained by the absorbent sheet.

17. System according to claim 16 including means for substantially separating the absorbent sheet and the first container one from another.

18. System according to claim 16 or 17 including means for drying the absorbent sheet thereby retaining at least a portion of the substance on the absorbent sheet.

19. System according to any of claims 16 to 18 including means for affixing the absorbent sheet to a further container, the further container having a plurality of wells formed therein.

20. A substance removed from a container using the method claimed in any of 1 claims to 7.

21. A substance removed from a container using the apparatus claimed in any of claims 8 to 12.

22. A substance removed from a container using the system claimed in any of claims 16 to 19.

23. Method substantially as described herein with reference to Figures 2 to 6 of the accompanying drawing.

24. Apparatus substantially as described herein with reference to Figures 1 to 6 of the accompanying drawing.

Fig.1.

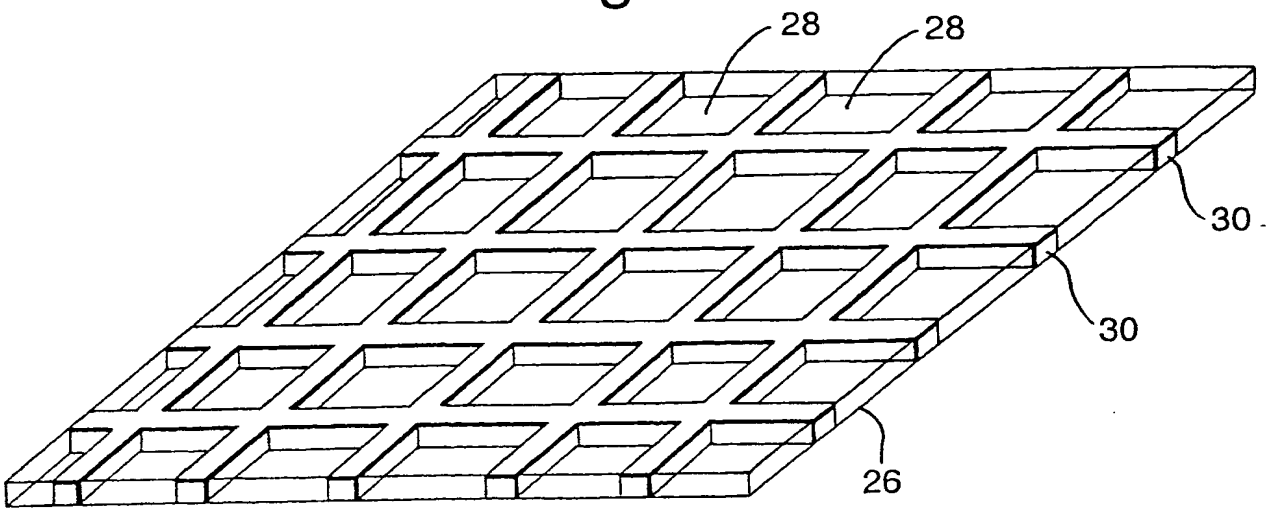


Fig.6.

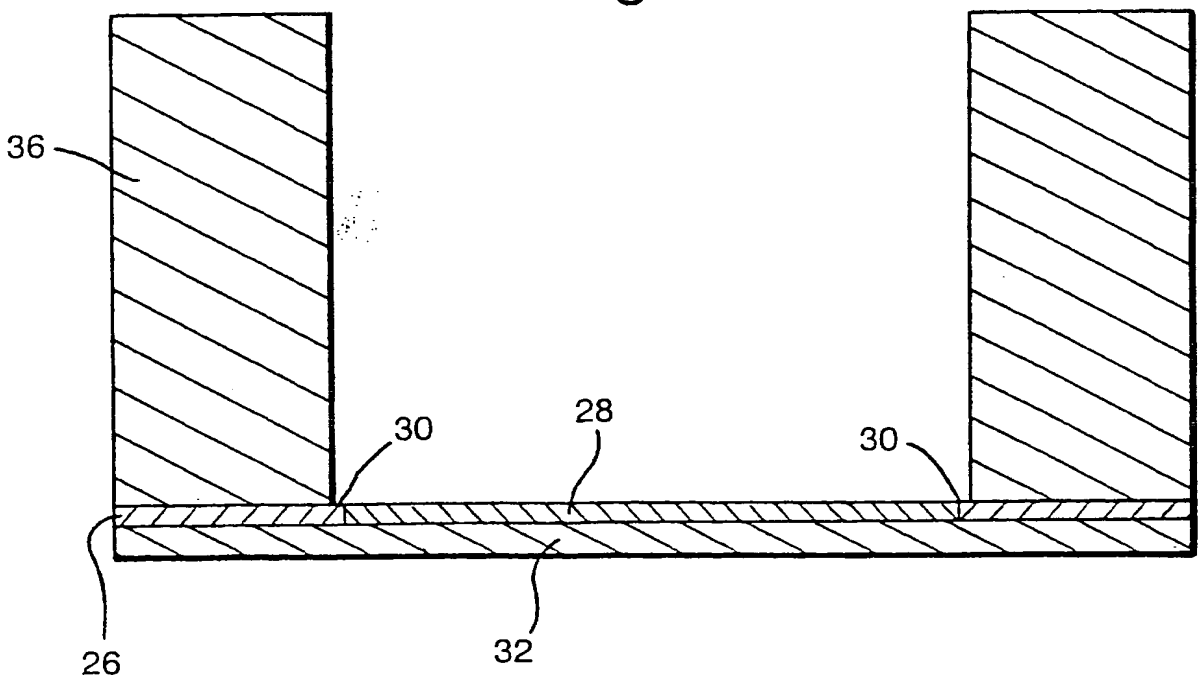


Fig.2.

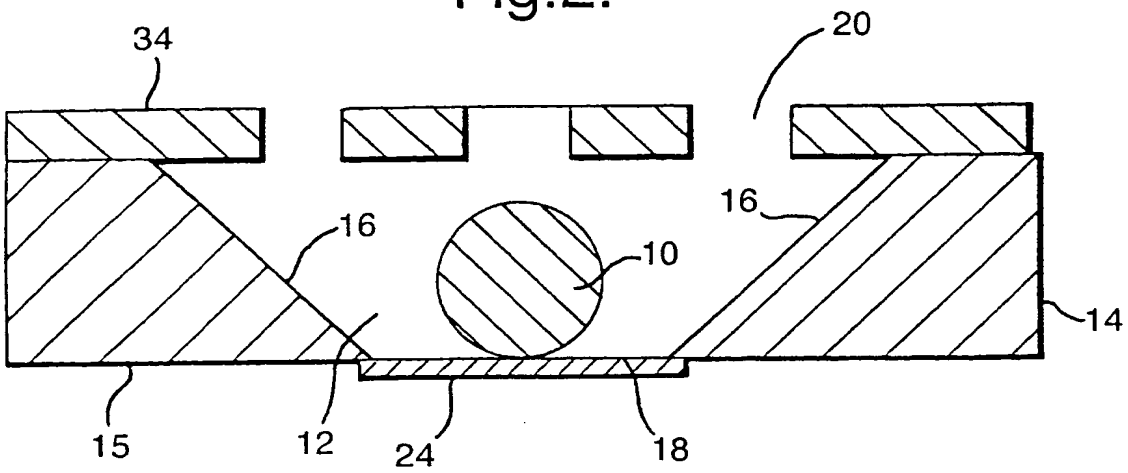


Fig.3.

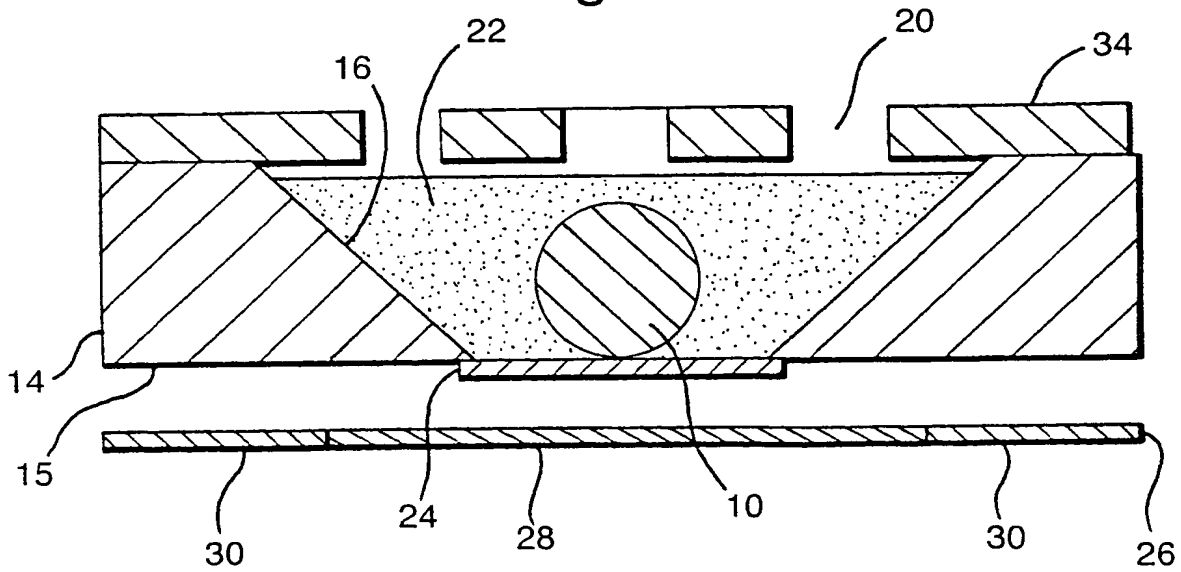


Fig.4.

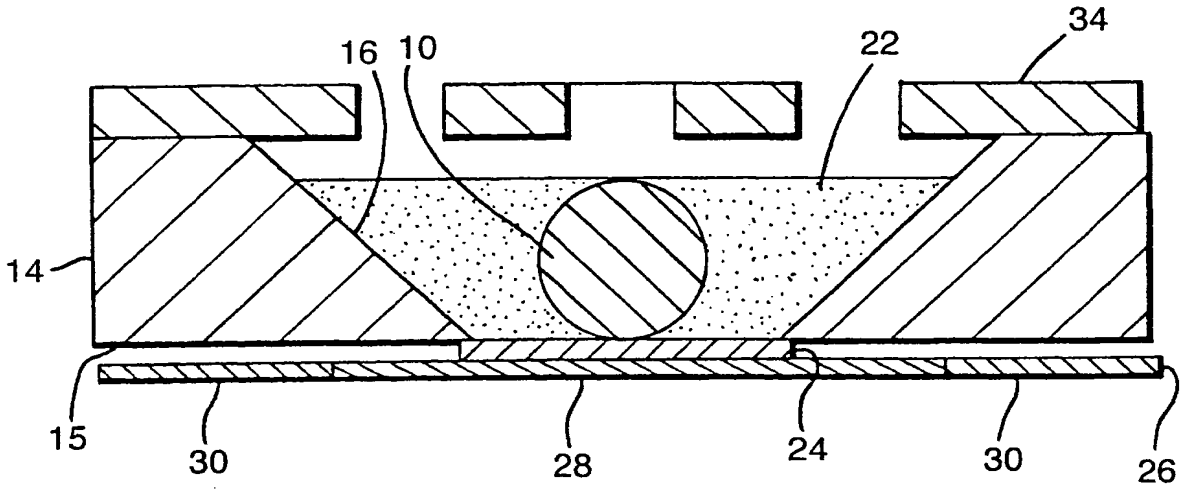
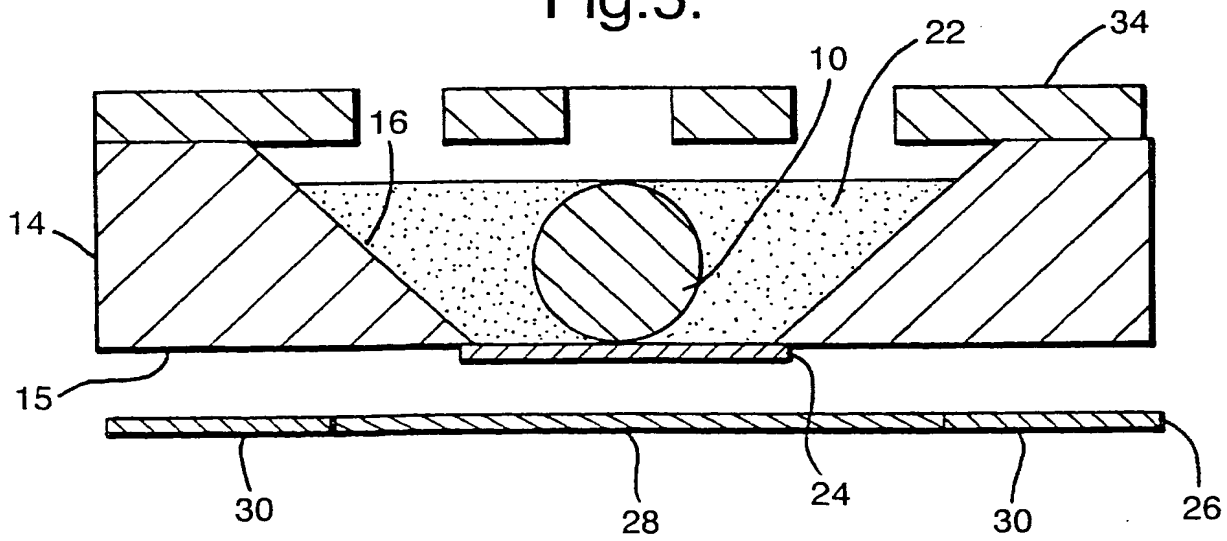


Fig.5.



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(75) Inventor/Applicant *(for US only)*: **CORLESS, Anthony, Robert** [GB/GB]; Schillings, Pound Farm Lane, Ash GU12 6EG (GB).

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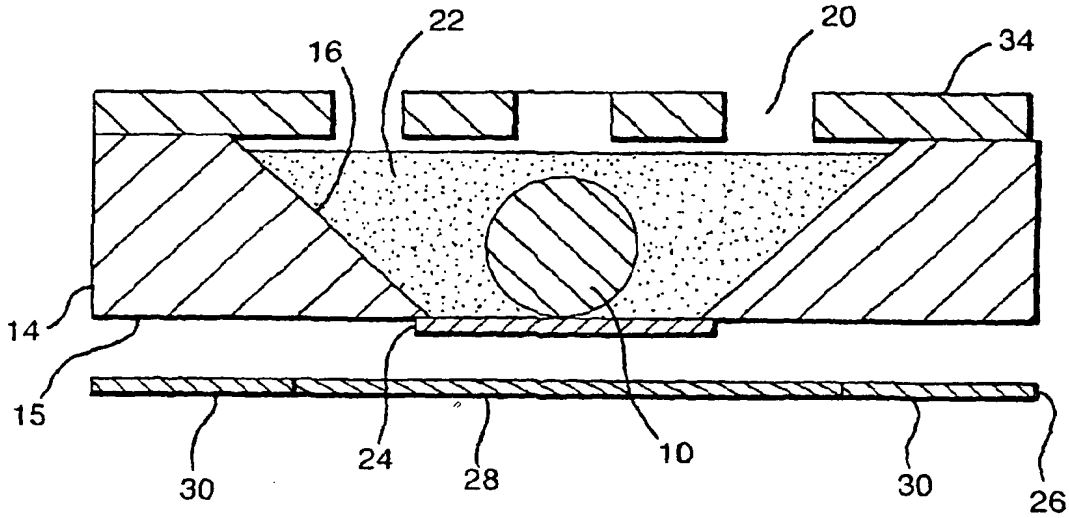
(54) Title: METHOD OF AND APPARATUS FOR REMOVING A SUBSTANCE FROM A CONTAINER



(57) Abstract: A bead (10) holding a chemical compound is situated in a well (12) of a micro-titre plate (14). A liquid (22) is introduced into well (12) and the chemical compound is released into the liquid. The liquid (22) and the chemical compound may be removed from the well (12) by bringing a capillary membrane (26) into contact with the well (12). Liquid (22) is drawn into the capillary membrane (26) via capillary action. Membrane (26) has areas of hydrophobicity (30) defined thereon so that the liquid (22) and the compound are drawn into predefined areas of the membrane (26). The membrane (26) can be dried and rehydrated at a later date in order to screen the compounds for activity, or it may form the base of an array of wells of a further micro-titre plate. Screening for compounds of interest may then take place either on the sheet, or with the sheet forming the base of the further micro-titre plate.

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For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

INTERNATIONAL SEARCH REPORT

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A. CLASSIFICATION OF SUBJECT MATTER
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According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 B01J G01N B01L

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 98 24543 A (BINNIE ALASTAIR ;GLAXO GROUP LTD (GB); SUGARMAN JEFFREY HOWARD (US) 11 June 1998 (1998-06-11) page 7, line 22 -page 8, line 32 page 9, line 25 - line 32 page 23, line 14 - line 35; claims 1,8-10,17,25; figures 3,5A,5F	1,7, 13-15, 20-22
X	WO 95 01559 A (EIGEN MANFRED ;HENCO KARSTEN (DE); THUERK MARCEL (DE); DOERING MIC) 12 January 1995 (1995-01-12) page 4, line 5 - line 23; figure 14	1,7,13, 20-22
X	US 4 264 560 A (NATELSON SAMUEL) 28 April 1981 (1981-04-28) column 6, line 47 -column 9, line 17	8,9, 20-22
A	column 12, line 22 -column 13, line 33; figures 2,5	1-7

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[X] Further documents are listed in the continuation of box C.

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"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
16 March 2000	20/09/2000

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Veefkind, V

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Internatiq Application No
PCT/GB 99/03278

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	WO 98 15355 A (DANNOUX THIERRY L A ;CORNING INC (US)) 16 April 1998 (1998-04-16)	20-22
A	the whole document	1-12
X	DE 24 24 426 A (GASBARRO LUCIANO DR) 6 March 1975 (1975-03-06)	8-10
A	page 4 -page 5 page 8 -page 9; claims 1-6; figures 1-4	1-5
X	WO 97 15394 A (BAINS WILLIAM ARTHUR ;HOUZEGO PETER JOHN (GB); SMITHKLINE BEECHAM) 1 May 1997 (1997-05-01) cited in the application page 1 -page 10; figures 1,2	13,14, 20-22
A	DE 196 28 928 A (BASF AG) 22 January 1998 (1998-01-22) the whole document	4,8-12

INTERNATIONAL SEARCH REPORT

International application No.
PCT/GB 99/03278

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☒ Claims Nos.: 23,24
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

According to Rule 6.2.(a) PCT a claim shall not, in respect to the technical features of the invention, rely on references to the description or drawings.

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

1-15,20-22

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

1. Claims: 1-15,20-22

1.1. Claims: 1-12
Independent claim 1 and dependent claims 2-7 describe a method of removing a substance from a container by: a) introducing a liquid to take up at least a portion of the substance and b) removing fluid and substance by placing a sheet of adsorbent material in suffciently close proximity so they are absorbed and retained.
Independent claim 8 and dependent claims 9-12 describe an apparatus for removing a substance from a container, comprising an absorbent sheet having defined thereon a plurality of hydrophilic regions whose boundaries are defined by hydrophobic portions, suitable for receiving contents from a plurality of wells formed in the container.

1.2. Claims: 13-15
Independent claim 13 and dependent claims 14 and 15 relate to a container comprising a plurality of wells, the base of a well having at least one aperture, dimensioned to retain liquid by way of surface tension.

1.3. Claims: 20-22
Independent claims 20, 21, and 22 relate to three substances, obtainable by removing them from a container.

2. Claims: 16-19

Independent claim 16 and dependent claims 17-19 relate to a system for removing a substance from a container, comprising locating means for an article, placing means for placing article in container, fluid introduction means, chemistry releasing means, and means to bring absorbent close to well in container.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 23,24

According to Rule 6.2.(a) PCT a claim shall not, in respect to the technical features of the invention, rely on references to the description or drawings.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Internatio pplication No
PCT/GB 99/03278

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